39. (Once amended) An antibody that binds specifically to the polypeptide shown in Figure 2 (SEQ ID NO: 2).

Remarks/Arguments

The foregoing amendments in the specification and claims are of formal nature, and do not add new matter. In particular, the amendments to the specification serve to provide a more specific title, to remove the hyperlinks embedded in the specification, and to update the address of ATCC.

Prior to the present amendment, claims 39-44 were pending in this application and were rejected on various grounds. Claim 44 has been cancelled, and claim 39 has been amended. The rejection of claims 39-43 is respectfully traversed.

Priority

Based on the ability of the PRO211 to inhibit VEGF stimulated proliferation of adrenal cortical capillary endothelial cells, which was disclosed in application PCT/US00/04414, the Examiner accorded February 22, 2000 as the earliest priority date to the present application. As discussed in the arguments below, the gene amplification data, which provide patentable utility for the anti-PRO211 antibodies claimed, were first disclosed in application PCT/US98/18824, filed on September 10, 1998. Accordingly, the effective priority date of the present application is September 10, 1998.

Applicants note that a concise priority claim was entered into the present application with a Preliminary Amendment filed on August 19, 2001.

Specification

The specification has been objected to for containing embedded hyperlink and/or other form of browser-executable code. Applicants were further requested to correct at typographical error at page 202, line 37, and to update the address of ATCC. The foregoing amendment are believed to overcome all objections.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claims 39, 44, and dependent claims 40-43 have been rejected, since the Examiner found the difference between "binding" and "specific binding" unclear. Claim 44 has been cancelled, and claim 39 has been amended to recite specific binding. As all claims pending refer to specific binding, there is no ambiguity in the claim language, and the present rejection should be withdrawn.

Claim Rejections - 35 U.S.C. §102

Claims 39-44 have been rejected under 35 U.S.C. 102(a) as allegedly being anticipated by WO 99/58660 (Ruben et al., November 18, 1999). Since the effective filing date of the present application is September 10, 1998, Ruben et al. is not a valid reference, and the present rejection should be withdrawn.

Claim Rejections - 35 U.S.C. §103

Claims 30-44 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over EMBL U48852, in view of Sibson et al. (WO 94/01548_ and Godowshi et al. (US Patent No. 6,030,831). AMBL U48852 provides a hamster sequence, with 1037 matches out of 1364 bases, i.e. having about 76% sequence amino acid sequence identity with the PRO211 polypeptide of the present invention. According to the rejection, at the time the present invention was made "[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make an antibody, including an labeled, humanized or monoclonal antibody or antibody fragment to the polypeptide of EMBL U48852 because Sibson outlines the uses, advantages and general methods of making antibodies to proteins encoded by expressed nucleic acids and Godowsi et al. teach a variety of antibody types and methods of making and using them." The Examiner adds that one would have been motivated to make such antibodies to use in protein localization or purification, for example.

Applicants respectfully disagree, and vigorously traverse the rejection.

The claims in the present application are directed to antibodies which specifically bind to a PRO211 polypeptide of SEQ ID NO: 2.

The polypeptide of SEQ ID NO: 2 is novel, and unobvious.

As noted before, Applicants rely on the gene amplification data provided in Example 92 to establish a specific, substantial and credible asserted utility for the PRO211 polypeptides.

Gene amplification is an essential mechanism for oncogene activation. It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis. As described in Example 92 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 8 (pages 230-234 of the specification), including primary lung cancers and colon cancers of the type and stage indicated in Table 8 (page 227). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 222, lines 34-36). Gene amplification was monitored using real-time quantitative TaqMan™ PCR. The gene amplification results are set forth in Table 9. As explained in the passage bridging pages 222 and 223, the results of TaqMan™ PCR are reported in ΔCt units. One unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold, etc. amplification. PRO211 showed 2-3 fold gene amplification in a number of lung and colon tumors.

The attached Declaration by Audrey Goddard clearly establishes that the TaqMan™ real-time PCR method described in Example 92 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results set forth in Table 9 one of ordinary skill would find it credible that PRO211 is a diagnostic marker of human lung and colon cancer. Accordingly, antibodies specifically binding to a PRO211 polypeptides find utility in the diagnosis of cancer, e.g. lung or colon cancer.

Before the present invention was made, nobody could have contemplated the existence of a PRO211 polypeptide, and nobody would have expected that such polypeptide, if existed, would be associated with the formation of lung or colon tumor. Indeed, EMBL U48852 has a limited degree of sequence identity with the PRO211 polypeptide of the present invention. The cited references, when taken alone or in combination, provide no suggestion or hint that the EMBL U48852 polypeptide would be associated with cancer, or would otherwise have biological properties similar to those of PRO211. As a result of the unexpected and unanticipated property

of the polypeptide to which they bind, the antibodies of the present invention have the unobvious property of being able to diagnose cancer, in particular lung or colon cancer. Since this property is not disclosed or suggested in the cited references, or their combination, the present rejection is believed to be misplaced, and should be withdrawn.

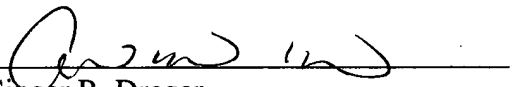
Attached hereto is a marked-up version of the amendments made to the specification and claims, entitled "**Version with markings to show changes made.**"

All claims are believed in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No: 39780-1618P2C6). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Dated: March 14, 2003

By: 

Ginger R. Dreger
Registration No. 33,055
Attorney of Record

HELLER ERHMAN WHITE & McAULIFFE LLP
Customer No. 35489
275 Middlefield Road
Menlo Park, CA 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

Version with markings to show changes made

In the Specification:

The original title has been canceled, and replaced with the following new title: ---- Anti-PRO211 polypeptide antibodies.--

The paragraph, beginning at page 69, line 6, has been amended as follows:

--Percent amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). [The NCBI-BLAST2 sequence comparison program may be downloaded from http://www.ncbi.nlm.nih.gov.] NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.--

The paragraph, beginning at page 71, line 26, has been amended as follows:

--Percent nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). [The NCBI-BLAST2 sequence comparison program may be downloaded from http://www.ncbi.nlm.nih.gov.] NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.--

The paragraph beginning at page 147, line 27, has been amended as follows:

The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included public databases (e.g., Dayhoff, GenBank), and proprietary databases (e.g. LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altschul, and Gish, Methods in

Enzymology 266: 460-80 (1996)[; http://blast.wustl/edu/blast/README.html]) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons with a Blast score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

The paragraph, beginning at page 154, line 14 has been amended as follows:

--The EST sequence accession number AF007268, a murine fibroblast growth factor (FGF-15) was used to search various public EST databases (e.g., GenBank, Dayhoff, etc.) The search was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)[; http://blast.wustl/edu/blast/README.html]] as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. The search resulted in a hit with GenBank EST AA220994, which has been identified as stratagene NT2 neuronal precursor 937230.--

The paragraph beginning at page 167, line 30, has been amended as follows:

--The extracellular domain (ECD) sequences (including the secretion signal, if any) of from about 950 known secreted proteins from the Swiss-Prot public protein database were used to search expressed sequence tag (EST) databases. The EST databases included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequence. Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington[; http://bozeman.mbt.washington.edu/phrap.docs/phrap.html]).

The paragraph beginning at page 178, line 14, has been amended as follows:

--The extracellular domain (ECD) sequences (including the secretion signal, if any) of from about 950 known secreted proteins from the Swiss-Prot public protein database were used to search expressed sequence tag (EST) databases. The EST databases included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequence. Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington[; http://bozeman.mbt.washington.edu/phrap.docs/phrap.html]).--

The paragraph starting at page 202, line 37 has been replaced with the following rewritten paragraph: --A variety of protocols for measuring soluble or membrane-bound PRO317, using either polyclonal or monoclonal antibodies specific for that PRO317, are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), radioreceptor assay (RRA), and fluorescent activated cell sorting (FACS). A two-site monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on PRO317 is preferred, but a competitive binding assay may be employed. These assays are described, among other places, in Maddox *et al.* J Exp. Med., 158:1211 (1983).--

The paragraph starting at page 250, line 1 has been replaced with the following new paragraph:: -- The following materials have been deposited with the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209(ATCC):

Material	ATCC Dep. No.	Deposit Date
DNA32292-1131	ATCC 209258	September 16, 1997
DNA33094-1131	ATCC 209256	September 16, 1997
DNA33223-1136	ATCC 209264	September 16, 1997
DNA34435-1140	ATCC 209250	September 16, 1997
DNA27864-1155	ATCC 209375	October 16, 1997
DNA36350-1158	ATCC 209378	October 16, 1997
DNA32290-1164	ATCC 209384	October 16, 1997
DNA35639-1172	ATCC 209396	October 17, 1997

DNA33092-1202	ATCC 209420	October 28, 1997
DNA49435-1219	ATCC 209480	November 21, 1997
DNA35638-1141	ATCC 209265	September 16, 1997
DNA32298-1132	ATCC 209257	September 16, 1997
DNA33089-1132	ATCC 209262	September 16, 1997
DNA33786-1132	ATCC 209253	September 16, 1997
DNA35918-1174	ATCC 209402	October 17, 1997
DNA37150-1178	ATCC 209401	October 17, 1997
DNA38260-1180	ATCC 209397	October 17, 1997
DNA39969-1185	ATCC 209400	October 17, 1997
DNA32286-1191	ATCC 209385	October 16, 1997
DNA33461-1199	ATCC 209367	October 15, 1997
DNA40628-1216	ATCC 209432	November 7, 1997
DNA33221-1133	ATCC 209263	September 16, 1997
DNA33107-1135	ATCC 209251	September 16, 1997
DNA35557-1137	ATCC 209255	September 16, 1997
DNA34434-1139	ATCC 209252	September 16, 1997
DNA33100-1159	ATCC 209373	October 16, 1997
DNA35600-1162	ATCC 209370	October 16, 1997
DNA34436-1238	ATCC 209523	December 10, 1997
DNA33206-1165	ATCC 209372	October 16, 1997
DNA35558-1167	ATCC 209374	October 16, 1997
DNA35599-1168	ATCC 209373	October 16, 1997
DNA36992-1168	ATCC 209382	October 16, 1997
DNA34407-1169	ATCC 209383	October 16, 1997
DNA35841-1173	ATCC 209403	October 17, 1997
DNA33470-1175	ATCC 209398	October 17, 1997
DNA34431-1177	ATCC 209399	October 17, 1997
DNA39510-1181	ATCC 209392	October 17, 1997
DNA39423-1182	ATCC 209387	October 17, 1997
DNA40620-1183	ATCC 209388	October 17, 1997
DNA40604-1187	ATCC 209394	October 17, 1997
DNA38268-1188	ATCC 209421	October 28, 1997
DNA37151-1193	ATCC 209393	October 17, 1997
DNA35673-1201	ATCC 209418	October 28, 1997
DNA40370-1217	ATCC 209485	November 21, 1997
DNA42551-1217	ATCC 209483	November 21, 1997
DNA39520-1217	ATCC 209482	November 21, 1997
DNA41225-1217	ATCC 209491	November 21, 1997
DNA43318-1217	ATCC 209481	November 21, 1997
DNA40587-1231	ATCC 209438	November 7, 1997
DNA41338-1234	ATCC 209927	June 2, 1998
DNA40981-1234	ATCC 209439	November 7, 1997
DNA37140-1234	ATCC 209489	November 21, 1997
DNA40982-1235	ATCC 209433	November 7, 1997

DNA41379-1236	ATCC 209488	November 21, 1997
DNA44167-1243	ATCC 209434	November 7, 1997
DNA39427-1179	ATCC 209395	October 17, 1997
DNA40603-1232	ATCC 209486	November 21, 1997
DNA43466-1225	ATCC 209490	November 21, 1997
DNA43046-1225	ATCC 209484	November 21, 1997
DNA35668-1171	ATCC 209371	October 16, 1997
DNA77624-2515	ATCC 203553	December 22, 1998--

In the Claims:

Claim 44 has been cancelled.

Claim 39 has been amended as follows:

39. (Once amended) An antibody that binds specifically to the polypeptide shown in Figure 2 (SEQ ID NO: 2